NATIONAL INSTITUTES OF HEALTH

FISCAL YEAR 2005

PLAN FOR HIV-RELATED RESEARCH

IV: VACCINES

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

OFFICE OF AIDS RESEARCH

AREA OF EMPHASIS

Vaccines

SCIENTIFIC ISSUES

National Institutes of Health (NIH) and public health officials worldwide have indicated that safe and efficacious vaccines are essential for the control of the global pandemic of AIDS. HIV vaccines could work in one of several ways to prevent HIV: to prevent infection, to prevent disease, and/or to prevent transmission. Over the past 7 years, the NIH has increased support for a broad program encompassing basic, preclinical, and clinical research on HIV/AIDS vaccines to its current level at more than four times the budget allocated in FY 1996. The first efficacy trial of a candidate HIV vaccine, a bivalent recombinant gp120 envelope protein, was successfully completed by a biotechnology company in 2002/2003. Unfortunately no protection was observed against HIV infection, which appears to be related to the limited breadth of the virus neutralization response raised by this vaccine product. Additional analyses of trial data and samples from this and related trials conducted by the NIH may provide clues to guide future studies. As a result of increased funding from the NIH in the area of basic vaccine research in AIDS, many new approaches to HIV vaccines are being studied in preclinical testing in animal models. Because of experience developed with some of the initial HIV vaccine candidates, new candidate HIV vaccine products are being developed more rapidly for clinical use, and up to 10 additional products or combinations of candidate vaccine products are expected to enter Phase I or Phase II safety and immunogenicity trials in human volunteers during the next 2 years. As promising candidates move further in the HIV vaccine pipeline, it will become increasingly important to expand the trained core of personnel

who are able to conduct HIV vaccine trials and to train interested and committed individuals in their communities to educate and counsel individuals who are at increased risk for HIV infection.

Vaccine Design

Basic research on the virus and on the human immune responses to HIV infection continues to provide the crucial foundation for the design and development of AIDS vaccine candidates. Building on the insights of recent basic research findings on the structural components of HIV, particularly those related to the HIV envelope, and studies on immune responses in small animals and nonhuman primates (NHPs), new vaccine candidates are being designed and tested. One of the major hurdles that has faced HIV vaccine design is the genetic diversity of HIV. To address this issue, vaccine candidates are being constructed based on isolates from many regions of the world and several research groups are exploring mixtures of viral components from different isolates and clades. Other groups are attempting to identify natural variants that express envelope epitopes for neutralization that are seen on a wide range of strains. In addition, concepts that generate genetic copies of HIV that represent either a consensus of the genetic sequences for some HIV subtypes or ancestral HIV for the main, M group of HIV-1 strains are being explored. Others are seeking to identify or develop HIV envelope structures which either expose selected critical epitopes or are more broadly immunogenic than the original constructs of envelope gp120 that have been tested in clinical trials. In addition, several newer vaccine strategies are using different adjuvants, immune modulators, and other delivery components to optimize the immune responses that are generated by the HIV vaccine candidates. Basic studies of the mechanisms of antigen presentation and design of vaccines to engage the most effective antigen presentation are ongoing.

Animal Model Development and Testing of Vaccines

Suitable animal models, especially NHPs, are crucial to the development and preclinical testing of new concepts in HIV/AIDS vaccine candidates. Because HIV does not replicate in monkeys without adaptation, simian immunodeficiency virus (SIV) or recombinant chimeric simian/human immunodeficiency viruses (SHIV) with HIV envelope inserted into an SIV backbone have been used in a number of vaccine studies. The initial pathogenicity and vaccine studies with SHIV viruses have revealed a number of limitations, and newer versions of this type of recombinant or chimeric viruses are now being studied for pathogenicity and ease of transmission. One of the primary concerns is that the highly pathogenic recombinant

SHIV viruses do not reflect the normal slow progressive loss of CD4 T cells seen in HIV-infected persons. Thus it appears easy for vaccines to induce some immune protection from disease progression with even a modest impact on the initial viral replication. Unfortunately, the SIV viruses, which more closely mimic HIV disease progression, do not permit an effective evaluation of candidate HIV vaccines that incorporate HIV envelope components. Newer SHIV stocks of virus, which have been derived from recently transmitted HIV or HIV isolates using CCR5 chemokine receptors that are classified as macrophage-tropic, are being studied. In addition, SHIV strains that reflect the kinds of viral diversity seen in the global epidemic are being constructed and tested to prepare viruses for testing of vaccine strategies that incorporate diverse HIV envelope components. Several groups have been developing animal models to address questions of mother-to-child transmission (MTCT) of HIV both as models for passive immunity to address neonatal transmission and as infant models to address questions of vaccine-induced prevention of breastfeeding transmission.

The supply of NHP, particularly rhesus macaques, in sufficient quantities and with adequate space to house infected animals remain problematic for NIH-sponsored research. Priorities for testing vaccine and microbicide candidates not only for HIV/AIDS research, but also for biodefense research, continue to put pressure on the limited supply of monkeys and the available space for conducting experiments. This is particularly an issue for appropriate biosafety housing once vaccinated animals are challenged with viruses or other pathogens. The NIH is working with various research institutions and other organizations to find solutions to these obstacles.

Correlates of Immune Protection

AIDS vaccine research with at least limited protection using monkey models has provided strong scientific rationales to further explore and develop several vaccine concepts and to move additional vaccine candidates into clinical testing. However, there is, as yet, no single correlate of immune protection that can be used as a yardstick to compare the kinds of protection observed in different animal models. As research on HIV/AIDS vaccines progresses, the evidence is accumulating that the correlate of protection will be some complex of both cellular and humoral immunity. In parallel, additional basic research is needed to better understand what makes some individuals either resistant to infection when they are exposed to HIV or able to control the infection so that disease progression is slowed even without the use of antiretroviral therapy (ART). While some individuals with specific major histocompatibility genotypes are able to mount strong

protective immune responses, it is not clear whether vaccine candidates can induce these kinds of responses in the broader population at risk of infection. Also it is not clear which components of these immune responses are necessary and sufficient for protection. This poses a need to move candidate vaccines into human clinical trials to obtain some of these answers.

Clinical Trials and Site Development

Over the past 5 years, the HIV Vaccine Trials Network (HVTN) has expanded from the previous small number of domestic sites conducting Phase I and II vaccine trials that were present in the AIDS Vaccine Evaluation Group (AVEG) to a network, now consisting of 17 domestic and 17 international sites for the conduct of Phase I, II, and III clinical trials. Significant efforts are underway to identify populations and develop cohorts necessary to conduct large-scale clinical studies at these and additional sites. In some cases, these sites require substantial infrastructure development and capacity building to ensure that the clinical researchers, scientists, and medical personnel are appropriately trained to design, conduct, and analyze the clinical trials as full and equal partners. In addition, the active education and participation of the affected community in these efforts also is critical.

The NIH has now conducted, in collaboration with academic researchers and industry co-sponsorship, more than 50 Phase I and 3 Phase II clinical trials of more than 30 vaccine products, individually or in combination, in human volunteers. Although production of some new candidate vaccines for clinical study has proceeded slowly, at least 10 new candidate vaccines will enter Phase I trials during the next 2 years. Several new combinations of products, which are expected to provide even better immune responses in combination, will also be tested in Phase I or II trials. Initial studies are leading to more advanced vaccine candidates that may provide better protection from HIV transmission. The Dale and Betty Bumpers Vaccine Research Center recently launched the first Phase I clinical trial of a multi-clade, multi-gene DNA vaccine candidate. In addition, since January 2003, three vaccine candidates supported through NIH grants or contracts have entered trials in the United States and/or in international sites. Sites in Haiti, Trinidad and Tobago, Brazil, and Peru are now completing a Phase I/II study that was conducted in parallel with studies in the United States on recombinant avipox products. Sites in Botswana and South Africa are expected to initiate Phase I trials of new products in 2003 in parallel with studies in selected sites in the United States. A Phase II trial of a recombinant adenovirus product from Merck will be initiated in 2003. In partnership with the Government of Thailand and the Department of

Defense, Walter Reed Army Institute of Research, the NIH will support a large Phase III trial of the "prime-boost" concept utilizing an avipox recombinant vector (ALVAC - vCP1521) from Aventis to prime the T-cell components of the immune response to HIV structural proteins and a bivalent B/E recombinant gp120 envelope protein product (AIDSVAX B/E) from VaxGen to boost immune antibodies to the envelope.

The NIH will continue to place a high priority on the development and testing of AIDS vaccine candidates and provide support for the basic research needed to continue to fill the AIDS vaccine pipeline.

FY 2005 PRIORITIES FOR HIV/AIDS VACCINES

Several priority areas previously identified in the *FY 2004 NIH Plan for HIV-Related Research* have been revised and modified or focused to more specifically address critical needs. These are listed below, in priority order.

PRIORITY FOR FUTURE RESEARCH

Accelerate the development of new candidate vaccines into clinical trials.

This priority is expanded below to summarize three key points that need particular emphasis to accelerate the entry of candidate vaccines into clinical trials.

- **To accelerate vaccine candidates from concept to clinical trials, the NIH should identify ways to centralize or partially centralize and/or streamline efforts and to develop a systematic approach to make and qualify products, produced under good laboratory practice (GLP) and good manufacturing practice (GMP), for testing in both preclinical and initial clinical studies.**

Concerns have arisen that developing mechanisms or setting up individual contracts on a per product basis substantially lengthens product development timelines, because new groups, particularly those composed of academic investigators and/or small biotechnology companies, repeatedly encounter obstacles and address issues previously encountered and resolved by other more experienced groups. Specifically, use of industrial experience that has been developed in protein production, vector production, DNA construct development, and process development should shorten the timelines. This will be particularly useful for academic investigators who are encountering many of the issues of product development and preparation of investigational new drug (IND) applications for the first time. For more complex products that require significant biological and/or biochemical process development to characterize and qualify lots, interactive support is needed on a continuing

basis to provide stable, ongoing expertise. Toxicology and safety testing alone can extend timelines for 2 years, so incentives should be developed for vaccine designers to discuss required qualifying tests with the NIH and the Food and Drug Administration (FDA) early in the process.

- **Comparative studies are needed in preclinical evaluation of HIV vaccine candidates. To support comparative vaccine studies and other HIV/AIDS work, standardized, validated assays with reagents of known identity and source are absolutely essential. A panel of immunological assays should include expanded assessment of cellular immunity and neutralizing antibodies, reagents to test specific responses, and easy access for both academic and industrial investigators to a standard panel of viral isolates for testing intersubtype and intrasubtype viruses. Continuation of the cross-Agency team that has developed to evaluate assay performance under GLP regulations in different labs for ELISPOT is encouraged and should be formally supported and expanded to incorporate additional cellular and humoral immunity assays.**

Data from animal models where protection has been achieved indicate that current assays for cytotoxic T lymphocytes (CTL) may not be predictive of protection from disease. Therefore, additional cellular immunity assays for analysis of components of the immune system must be developed and testing expanded. Additional concerns about the development of an array of similar or related products with little or no comparative data between products as well as to other products sometimes leaves the NIH with a limited basis on which to select and move one or more products into clinical testing. Tests for neutralizing antibodies often are analyzed with only a few clinical isolates that are available to an individual investigator or company. A panel of isolates that are available to all investigators should be developed, and resource laboratories that can conduct validated neutralization assays in rapid throughput should be designated. While NHP studies are not required by the FDA for movement of products into Phase I clinical testing, animal testing should be refined so that at least one small animal model is consistently used for comparative immunogenicity data and investigators developing vaccines should be encouraged to conduct studies in this species early in the analysis of their product. Protection and strong immunogenicity in NHP will undoubtedly be a driving force to move products beyond Phase I trials in humans. Thus, access to NHPs for comparative study is essential as early as possible in testing so that these studies can be performed at least in parallel with initial human trials.

- **Continue to support basic research to feed new products into the vaccine pipeline.**

There is no certainty that HIV/AIDS vaccine concepts currently in clinical trials or in product development will realize the quest for an HIV vaccine. Indeed, we currently are faced with the failure of the first large Phase III trial to provide broad protection against HIV infection and the likelihood that candidate vaccines in the next Phase III trials, which are focused on induction of cellular immunity, are more likely to delay disease progression. Thus an urgency exists to pursue additional, more highly effective vaccine designs to prevent HIV infection through continuing support for Innovation Grants (R21) and HIVRAD (R01) programs. This will provide a strong research base for continual development of new vaccine concepts. It is critically important to continue an emphasis on ways to induce broadly cross-reactive HIV neutralizing antibodies.

PRIORITY FOR FUTURE RESEARCH

- **Design and conduct clinical trials with special attention to the issues of immunologic serotypes, genetic variants, and their importance to vaccine design. Incorporate the testing of vaccines representing different immunotypes in populations where intersubtype and multiple genetic subtypes are present.**

Phase I and II trials are being initiated with vaccine candidates representing several clades, various individual clades and potentially differing serotypes within the B and C clades. Through the HVTN and other mechanisms, the NIH plans to support trials to assess responses to HIV isolates induced by vaccine candidates representing different genetic clades either individually or in multi-clade vaccine designs. A concerted effort is needed to assess and define serologic immunotypes of envelope recognized by vaccinees. Studies should be designed to determine whether multi-clade responses and/or selective cross-reactive immune responses to conserved envelope motifs are needed for effective HIV vaccine induction of broadly neutralizing immune responses. The extent of cross-reactive cellular responses should also be evaluated. Efficacy trials to evaluate vaccine products in different risk populations will require a significant expansion of the support for clinical trial sites in the United States and at international locations.

PRIORITY FOR FUTURE RESEARCH

- **Continue and expand the initial efforts to educate high-risk populations and communities about HIV vaccines. In particular, continue to develop tools, devise outreach programs, and implement**

strategies to involve adolescent populations in HIV vaccine trials that will be testing products for efficacy.

Health disparities exist at many levels in the United States and even more so in the international arena. Recent studies have led to appreciation of the fact that communities which do not participate in clinical trials may often be the last to benefit from medical advances. Because some of the highest risk populations for HIV infection are adolescents, minorities, youth, and women, it is imperative that HIV vaccine trials be inclusive of all populations where benefit might be derived. In addition to broad outreach and community education, one of the concepts that has been raised for consideration is that young persons from minority communities, particularly those in institutions of higher learning, might be trained in vaccine information to serve as community health leaders. These young people are often informed through multiple sources and able to network to central information sources which are reliable, thus constituting a bridge to their wider communities. Because it will take time to establish trust in these communities, efforts to engage young people in these populations must begin now. There appears to be great value in conducting Phase I trials in selected populations, particularly in the international sites where future large-scale vaccine trials will be conducted, because it will train a core of individuals who will be training the next round of clinical vaccine researchers.

PRIORITY FOR FUTURE RESEARCH

- **Continue to support the development of breeding colonies, appropriate biosafety housing, and most effective use of specific pathogen-free (SPF) NHPs for HIV vaccine research and immunogenicity studies.**

Substantial progress analyzing vaccine concepts in NHPs, particularly rhesus macaques (specifically *Macaca mulatta*), has been made in the past several years due to new tools for measurement of viral load, assessment of immune responses, and new stocks of challenge virus that have been produced for shared use. There is a strong consensus to support NHP as key elements for evaluating vaccine design. Testing of vaccine concepts, through existing contracts of the Division of AIDS, National Institute of Allergy and Infectious Diseases, is available to NIH-funded investigators; however, information about this program and procedures for access should be made available repeatedly to vaccine grantees and potential industrial partners to keep the process open and transparent and available for comparative testing.

PRIORITY FOR FUTURE RESEARCH

- **Accelerate testing of vaccines and monoclonal antibody interventions in infants born to HIV-infected mothers in situations where breastfeeding cannot be avoided.**

Emerging issues of resistance to first-line ART for prevention of MTCT of HIV as well as continuing concerns about drug toxicities in antiretroviral therapies have encouraged a continuing evaluation of the possibilities of vaccines and passive immune protection in breastfeeding populations of infants. In addition, there have been several advances in production of monoclonal antibody (MAb) cocktails and slow but continued progress on vaccine designs that are safe and adaptable for infants.

PRIORITY FOR FUTURE RESEARCH

- **Address new challenges in testing, and diagnosis of HIV infection in vaccinated individuals**.

As more complex vaccines enter clinical testing, the likelihood of an individual in a vaccine trial testing serologically positive will be increased. This needs to be monitored closely, and new approaches for definitive diagnosis of HIV-infected vaccinees should be explored now. Because some of the newer HIV vaccine candidates will contain multiple viral components and involve boosting of serological responses, there is an increased likelihood that vaccinees will test positive in one or more of the licensed serological tests for HIV. Furthermore, because of the designs of the next group of candidate vaccines entering clinical trials, vaccinees who have intercurrent HIV infections may have very low or undetectable viral RNA levels. Thus new serologic or nucleic acid diagnostic tests for HIV infection need to be explored. This issue should be addressed across governmental agencies, public health agencies, and nongovernmental groups that will be testing vaccines to ensure that timely resolution of this issue occurs before large numbers of uninfected vaccinees encounter social difficulties because of their anti-vaccine responses.

A CROSSCUTTING PRIORITY FOR FUTURE RESEARCH

- **For vaccines, as well as other modes of prevention and therapy, training of staff at the clinical trial sites is imperative.**

Long-term support and training of staff to develop a core of investigators at all potential vaccine trial sites is essential, whether these sites are domestic urban populations with high minority representation or rural international populations. Trained staff recruited from the populations studied will be vested in the successful completion of ongoing studies and

will enable the NIH to ensure the scientific and ethical conduct of high-quality trials with high levels of retention and followup, adequate sample collection, and accurate data for analysis of trial results.

SCIENTIFIC OBJECTIVES AND STRATEGIES

OBJECTIVE - A:

Increase scientific knowledge through basic research on protective immune responses and host defenses against HIV to facilitate the development of vaccines and other biomedical intervention strategies to prevent and/or control HIV infection.

STRATEGIES:

- Define the mechanisms underlying protective systemic and mucosal immunity to HIV and other lentiviruses by pursuing research that includes the following areas of interest:
  - Determine the mechanisms of immunologically mediated control of infection with HIV and other related lentiviruses, including the role of antigen-specific and antigen-nonspecific cellular and humoral immunity in inhibiting viral replication to provide a basis for optimal vaccine design.
  - Define the structure-function relationships and the antigenicity and immunogenicity of HIV proteins, including transient or intermediate and conformational domains induced by virus interacting with CD4, chemokine, dendritic cell (DC) surface proteins and adhesion molecules, and other cellular receptors to improve vaccine designs to more effectively induce immune responses to block infection by active and passive immunity.
  - Define and characterize viral B-cell and T-cell epitopes that induce protective immunity in HIV or AIDS-related disease; utilize structural analysis of envelope to determine whether and how their immunogenicity can be improved and exploited in vaccine development.
    - Determine the mechanism of how HIV and related lentiviruses evade or escape from humoral and cellular arms of the immune response; design vaccine approaches to prevent this; and define conserved epitopes in which genetic substitutions cannot be tolerated by the virus.
    - Characterize pathways of antigen processing of HIV proteins, including envelope glycoproteins, for presentation by MHC class I and class II molecules. Investigate the interaction of HIV proteins with antigen processing mechanisms that enhance or inhibit specific epitope presentation to the immune system.

- Study the role of DCs in the induction of immunological memory and long-term protective function of different subsets of human lymphocytes in HIV-related disease and in response to vaccination; define factors that favor establishment and maintenance of memory cells able to generate effective recall to vaccine antigens, particularly HIV and related viral antigens, and development of long-term protective immunity, particularly in human subjects.
- Study the mechanism of action of vaccine adjuvants and enhanced modes of HIV and related lentivirus antigen presentation to induce different cytokine or chemokine responses, innate immunity, and host factors; carry out translational research in NHP and human vaccinees.
- Determine how chronic infection with one strain of HIV or related lentivirus, including attenuated viruses, confers protection against subsequent infection or reduces viral replication of a second pathogenic virus strain; define the properties of the virus and of the immune system that are responsible for lack of disease induction by attenuated viruses and protection from challenge with wild-type virus; and determine the protective mechanism, duration, and extent of cross-protection.
- Define the heterogeneity of specific responses to vaccine immunogens, particularly HIV, within diverse tissue compartments, and identify factors that confer protection from infection by various routes including vaginal, rectal, oral, and parenteral exposure.
- Determine which factors promote development of particular human effector cell types, promote production of antiviral substances including chemokines, or enhance non-antigen-specific protective mechanisms.
- Define the basis for adaptive, antigen-specific immune reactivity (humoral, cellular, and other) across divergent HIV types (clades and biological phenotypes or immunotypes); study clinical samples from human volunteers participating in vaccine trials to determine the extent of cross-reactive immune responses that can be achieved with different candidate vaccines.

- Determine whether HIV immune responses that can contribute to immune enhancement of viral replication *in vitro* can interfere with induction or propagation of vaccine-induced effector responses *in vivo*.

- Seek new clues for correlates of immune protection from HIV-infected or highly exposed but seronegative individuals, across the life span, and from lentivirus models that will provide the basis for further design of candidate vaccines by conducting the following research:

  - Study acutely infected individuals, exposed/seronegative, or possibly transiently infected humans (including uninfected children born to HIV-infected mothers, individuals with controlled therapy interruptions, HIV-infected individuals vaccinated with therapeutic vaccines while on antiviral therapy, and nonprogressors) to define immune responses to HIV-1 and HIV-2, potential vaccine-inducible host immune responses, and viral factors (or viral attenuations) that reduce the amounts of circulating virus and influence disease course.

  - Elucidate the functional mechanisms for protective immunity against HIV, including identification of specific responses by passive transfer of antibody or immune cells and deletion of selected immune subsets in NHP models.

  - Investigate the sequence of events required for mucosal transmission/infection of HIV and other lentiviruses at different portals of entry to define how and where specific immune effector mechanisms can impede viral entry and/or prevent establishment of infection.

  - Study mucosal immunity to viral antigens and other infectious pathogens in relevant animal models and humans to develop optimal vaccine strategies for HIV antigen delivery and effective immune-based prevention of HIV transmission.

  - Explore the molecular epidemiology, humoral, and cell-mediated immune responses to HIV-1; acquire clinical specimens from populations relevant to vaccine trials for laboratory studies; and acquire appropriate epidemiological information to enable interpretation of these analyses.

- Monitor the effects on immune activation with intercurrent sexually transmitted diseases (STDs), malaria, tuberculosis (TB), hepatitis B and C, other infectious diseases, and with administration of drugs of abuse or effects of ART on viral shedding in vaccinated subjects. Model these confounding elements in NHP.

- Develop *in vitro* experimental approaches for analysis of vaccine responses that will combine sensitivity, specificity, high throughput, and the ability to use small sample volumes; develop *in vitro* and *in vivo* tools to study systemic and mucosal immune mechanisms of control of virus for analysis of vaccinated individuals (across life span) and protected animals by undertaking the following research activities:

  - Develop and improve animal models of lentivirus infection that are practical and representative of the spectrum of HIV infections and development of AIDS, including use of appropriate HIV cellular receptors and different modes of transmission; develop genetically defined and histocompatible NHP models to facilitate immune cell transfer studies; in general, make models amenable to use in evaluating protection by vaccines and other biomedical interventions. This may be approached, in part, by a genetic sequencing, particularly of selected regions of the macaque genome.

  - Develop improved methodologies and assays to measure viral neutralization; explore the mechanisms of virus neutralization and the reason(s) for the relative difficulty to neutralize primary isolates.

  - Develop and standardize immunological reagents; standardize cell, fluid, and tissue processing to ensure viability and maintenance of functional capacity of cells and stability of factors in serum, plasma, and culture supernatants; and develop quality control procedures for collecting, processing, freezing, storage, recovery, viability, and shipping of samples that will be essential in large-scale trials.

  - Study the function of CD4 T cells, CD8 T cells, and viral suppressive immune responses; develop and adapt high-throughput assays with specificity for primary virus isolates; and make available those reagents required for vaccine-related studies.

  - Develop or improve sensitive quantitative measures of HIV (and simian immunodeficiency virus [SIV]) in body fluids and low-level tissue reservoirs, including genital secretions and breast milk, to assess the effectiveness of vaccines designed to lower viral load and interrupt transmission or prevent disease progression.

OBJECTIVE - B:

Design viral antigens, adjuvants, immunomodulators, and vaccine delivery methods that elicit long-lasting protective immune responses against a broad range of HIV isolates by applying findings from basic, epidemiologic, and clinical research; facilitate development and preclinical evaluation of vaccine strategies in laboratory studies and animal models; and foster early and continued collaboration between academicians, other Government agencies, nongovernment organizations (NGOs), and industry in the research and development of candidate vaccines to test a broad array of vaccine concepts and combinations of different approaches for development of potential HIV vaccine products, including vaccines for particular populations.

STRATEGIES:

- Multiple parallel approaches to development and testing of candidate HIV/AIDS vaccines will be investigated to provide complementary and comparative preclinical data on safety and immunogenicity questions about HIV vaccines. Such studies should achieve the following:
  - Support the design, development, production, and testing of novel HIV/AIDS vaccine candidates for safety and for their ability to elicit appropriate antiviral immune responses. This may include, but is not limited to:
    - Virus-like particles containing one or more virus proteins, peptides, or antigens;
    - Whole-inactivated HIV rendered noninfectious by chemical and/or genetically engineered deletions of pathogenic viral elements;
    - Naturally occurring and genetically engineered, live-attenuated strains of HIV;
    - DNA or RNA coding for viral proteins;
    - Live, recombinant viral and bacterial vectors engineered to express one or more HIV proteins with attention to vectors that might provide dual benefit for HIV and some other pathogen or to vaccine vectors that target mucosal immune responses;
    - Viral replicons or other strategies to target DCs;

- Recombinant HIV envelope protein subunits produced by a variety of methods, with an emphasis on retention or exposure (e.g., through deglycosylation) of critical nonlinear or conformational structural epitopes for induction of effective antibody responses;
- Structurally constrained HIV envelope fragments, peptides, mimetopes, or complex peptides capable of inducing and boosting cellular or humoral immunity to HIV; and
- Cell surface components carried on the viral surface.

- Foster collaboration between academic investigators, industry sponsors, the NIH, the U.S. Food and Drug Administration (FDA), other Government agencies, and NGOs on research and development of novel vaccine design concepts. These collaborations should
  - Enable production of pilot lots of vaccine candidates for testing in NHPs and human subjects;
  - Develop programs to design and conduct comparative testing of vaccine approaches with industry and academic partners that will permit long-term followup to assess disease progression in animal models; and
  - Develop infrastructure; address scientific, legal, ethical, and regulatory issues to foster and encourage participation by, and collaboration between, academic investigators, industry, affected communities and populations, and other agencies in the research, development, production, and clinical testing of candidate vaccines.
- Foster the development of vaccines to optimize characteristics appropriate for broad international use, including designs exhibiting low cost with ease of production, stability, and ease of administration. This may include
  - Combined use of two or more vaccine strategies with mixed modalities to boost the same component and/or to engage different components of the immune response; and
  - Multivalent vaccine candidates incorporating different genetic clades and/or antigenic types to increase breadth of immune responses.

- Support design, development, and incorporation of methods to improve or modulate immune responses (qualitatively or quantitatively) in vaccine approaches, including
  - Novel adjuvants and delivery methods that might enhance effective DC antigen presentation;
  - Agents that stimulate or modulate mucosal immune responses or other host defenses, including cytokines or chemokines;
  - Vaccines formulated with cytokines or incorporating cytokine genes in vectors or other biologically active molecules; and
  - Other novel strategies, including nutritional supplementation and treatment of underlying infections and/or diseases that might have an impact on vaccine responses.
- Evaluate the efficacy of vaccine and other immune prevention strategies in animal models of HIV and related lentiviruses by
  - Testing vaccine and other biomedical prevention strategies in animal models that most closely mimic HIV infection in humans;
  - Determining *in vitro* correlates of an *in vivo* protective immune response;
  - Determining the effect of vaccine formulation, site of delivery, and regimen, as well as the nature, timing, phenotype, and route of infectious virus challenge on the effectiveness of the vaccine-induced immunity;
  - Defining the impact of different vaccine approaches on kinetics of immune responses, kinetics and localization of viral replication, long-term followup of disease progression with low-level chronic infection and concomitant diseases (e.g., TB, hepatitis, or autoimmune diseases), and biologic characteristics of breakthrough virus including transmissibility;
  - Determining the impact of genetic factors and age on vaccine responses and on protection against virus at various challenge sites;
  - Studying the efficacy of the immune response in the face of viral mutation and variation; and

- Investigating vaccines and other biomedical prevention strategies with attention to potential co-factors such as integrity of the mucosal surface, changes in vaginal/cervical epithelium during puberty, hormonal changes during pregnancy, use of contraceptives or hormone replacement therapy, and presence of STDs; wherever possible, study potential concomitant effects on the genital tract immune system and inflammatory activity that might compromise integrity of the mucosal surface or the inductive ability of vaccines.

- Support development of reagents and standardized methods to assess specific vaccine-induced immune responses in animal models and humans, including infants, for both humoral and cellular aspects of systemic and mucosal immunity. This includes:
  - Developing and refining assays to distinguish between serological and cellular responses due to immunization and those due to viral infection;
  - Characterizing and evaluating the potential negative side effects of candidate vaccine designs, including the potential to increase the susceptibility to infection or the rate of disease progression in animal models;
  - Standardizing and validating assays to assess vaccine potency;
  - Standardizing and validating assays to be used as Phase III study endpoints; and
  - Abiding by GLP regulations to perform endpoint assays in support of product licensure and instituting quality assurance programs to assure sponsors and vaccine manufacturers that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with regulations stated in 21CFR part 58.

- Foster research on the safety and regulatory considerations of candidate HIV/AIDS vaccines in development
  - Whose production utilizes human-derived tumor cell and other continuous cell lines;
  - That utilize vectors that have the potential to integrate into the host chromosome or have the potential for chronic expression;

- That might have the ability to be generated as either replicating or nonreplicating vectors;
- That have the potential to cause autoimmunity or highly immunogenic anti-vector responses; or
- That overexpress potentially deleterious vector proteins.

OBJECTIVE - C:

Identify mechanisms of protective immunity to HIV in newborns and infants, and support the development of distinct study designs for safe and effective vaccine strategies and passive immune interventions, alone or in combination with other interventions, for preventing or controlling HIV infection in this population worldwide.

STRATEGIES:

- Investigate the unique immune status and develop immune interventions in both pregnant women and infants to interrupt HIV transmission. Active and passive HIV vaccine strategies need to be modeled and evaluated, particularly in infants, in parallel to studies in uninfected adults. To accomplish this goal, it is important to develop research that will achieve the following:
  - Develop relevant animal models of maternal-fetal and maternal-infant perinatal transmission that can
    - Determine preclinical safety and immunogenicity of various HIV vaccines and adjuvants, particularly in primates;
    - Determine safety of various monoclonal and polyclonal antibody preparations;
    - Determine the best immunization routes or protocols to induce antibodies in milk and other secretions;
    - Evaluate efficacy of vaccines and passive immunotherapy for prevention of perinatal or breastfeeding transmission; determine whether there is attenuation of disease progression among neonatal animals that become infected despite immune intervention; determine correlates of protective immunity; and
    - Evaluate the effect of antiviral drugs in combination with immune and behavioral prevention strategies.
  - Determine virologic and nonimmunologic host factors that influence transmission of HIV-1 from mother to infant that would have an impact on selection of viral antigens for the design of an HIV vaccine or for identifying the target of immune-based intervention to prevent perinatal transmission. This includes
    - Determining the importance of viral load and viral phenotypes and genotypes in perinatal or early infant HIV transmission and what viral factors are associated with differences in perinatal transmissibility;

        - Developing standardized methods to collect specimens and to detect, characterize, and quantify HIV in cervico-vaginal secretions and in breast milk to determine their potential relevance in mother-to-child transmission; and
        - Determining if virus in maternal genital secretions or breast milk is distinguishable from virus found in blood and which type is transmitted from mother to fetus and mother to infant.
    - Identify maternal and infant immune responses that might control viral replication in either the mother and/or the infant and prevent transmission of HIV or establishment of infection in infants.

- Define immune approaches that will provide specific and sustained protection against HIV transmission; develop the products necessary to achieve these goals; and develop the capacity to evaluate their safety in human subjects. This research includes the following activities:
    - Determine specific immune strategies for perinatal intervention that blocks interaction of HIV with its receptors and co-receptors and/or to target infected cells.
    - Characterize the transmitted viral strains and monitor changes that may occur in proposed trial sites; evaluate the impact that genetic polymorphism in different racial or ethnic backgrounds might have on receptor usage or immune responsiveness.
    - Evaluate, in Phase I and Phase II studies, the safety and immunogenicity of various HIV vaccines, adjuvants, vaccine administration regimens, and the pharmacokinetics of passive antibody preparations among both HIV-infected pregnant women and newborns exposed to HIV (born to HIV-infected women).
- Test the safety and efficacy of active and passive HIV vaccine interventions alone or in combination with other modes of intervention, particularly in international settings with high seroprevalence. This testing includes the following activities:
    - Identify and characterize the important issues to consider in the development of criteria for advancement of candidate vaccines, adjuvants, and passive antibody preparations from Phase I and Phase II to Phase III clinical trials in pregnant HIV-infected women and/or HIV-exposed children. These criteria should include evidence of therapeutic effectiveness in mothers in addition to prevention of infection in HIV-exposed children.

- Develop the capacity in domestic and foreign trial sites necessary to enroll mothers and infants in trials of both preventive and therapeutic vaccines, passive immunity, and other perinatal interventions with prospective long-term followup. For vaccines, this should include the assessment both of duration and breadth of detectable humoral immune responses and of memory or recall responses in the cellular immunity compartment(s).
- Conduct Phase III clinical trials for evaluation of efficacy of the most promising candidate vaccines and/or passive antibody preparations that meet established criteria in pregnant HIV-infected women and/or children exposed to HIV.
- Develop criteria to define infant infection status as a perinatal intervention trial endpoint in countries where breastfeeding is recommended despite maternal infection status, including type of diagnostic tests, timing of the tests, length of followup, and adherence to followup visits.
- Study viral isolates and the immune response in infants who become infected despite administration of active and/or passive immunization to evaluate the effects of immune intervention on the characteristics of transmitted (escape) virus and on the quality, quantity, and timing of the infected infant's antiviral responses.
- Study the impact of early ART interventions and HIV vaccines given while on effective ART, on the maintenance or regeneration of antiviral immune responses of HIV-infected infants.

OBJECTIVE - D:

Conduct Phase I, Phase II, and Phase III trials for safety, immunogenicity, and efficacy with suitable candidate vaccines or concepts in domestic and international settings.

STRATEGIES:

- Support the conduct of Phase I, II, and III clinical trials that will determine long-term and short-term safety, evaluate efficacy, and compare immunologic responses to different preventive vaccine candidates by evaluating a broad range of humoral, cell-mediated, and mucosal immune parameters. This includes the following tasks:
  - Design and conduct Phase I and Phase II trials using promising HIV vaccine candidates. Trials should test immunogenicity of vaccine concepts, and address questions about optimal vaccine strain selection (i.e., the properties of a strain [immunologic, genotypic, or phenotypic]) that make it optimal for use in a selected population. Trials also should include an appropriate representation of ethnic and racial minority populations affected by HIV and be of an appropriate size to provide data on the frequency, magnitude, and breadth of immune responses to facilitate decisions regarding initiation and evaluation of larger "proof of concept" or efficacy trials.
- Develop a comprehensive plan for conducting vaccine trials with a high level of retention and adequate followup of vaccinees to reach predefined endpoints, as follows:
  - Prepare for adequate long-term followup of volunteers in HIV vaccine clinical trials to determine the durability of immune responses and protection, the correlates of immune protection, long-term safety, behavioral factors to influence adherence of followup visits, the impact of participation on risk-taking behavior, and vaccine-related reduction (or enhancement) of disease progression and HIV transmission.
  - Conduct large-scale efficacy trials of preventive vaccine candidates that have proven promising, safe, and immunogenic in Phase II trials and that meet appropriate criteria by
    - Evaluating HIV vaccine candidate efficacy against infection, disease, and/or transmission;
    - Evaluating additional virologic, immunologic, and behavioral outcomes, particularly potential correlates of protective immunity;

- Ensuring that trials are conducted with the highest regard for social, legal, and ethical standards and in populations that reflect the racial and ethnic burden of the HIV disease;
- Ensuring access to achievable, sustainable, and culturally appropriate best practices to prevent HIV exposure; and
- Developing, adapting/modifying, and coordinating educational and information programs about HIV and HIV vaccines suitable for the individual participants and communities of different ethnic, racial, and cultural backgrounds that will be involved in trials.

- Characterize the clinical course, immune responses, and other characteristics of vaccinees (e.g., behavioral risk of infection) who become HIV-infected; isolate and characterize viral isolates from participants in vaccine trials with intercurrent HIV infections to explore the possible effects of vaccination on the characteristics of escape (transmitted) viruses.
- Continue to use existing strategies to avert social harm and develop additional strategies to complement existing mechanisms at the local and national levels to reduce the risk of social and economic harm to volunteers in Phase I, II, and III trials and assist in providing solutions.
- Conduct behavioral risk assessment research during vaccine trials, particularly with Phase II and Phase III trial participants, to identify and evaluate any changes in risk behavior as a result of participation in a vaccine trial; develop, test, and ensure access to interventions to prevent high-risk behaviors; conduct behavioral research with specific emphasis on individuals who become infected during trials to identify interventions that may prevent high-risk behaviors in future trials or application of HIV vaccines.
- Closely coordinate the evaluation of research findings on prophylactic AIDS vaccines with preclinical research and immunotherapeutic interventions.

OBJECTIVE - E:

Develop strategies, infrastructure, and collaborations with researchers, communities, other U.S. Government agencies, other Governments, international and domestic NGOs, and industry that are necessary to ensure adequate performance of vaccine trials, while balancing the prevention needs of the at-risk populations; identify domestic and foreign populations; and perform necessary research to define seroincidence and viral subtypes and to determine and optimize feasibility of vaccine studies in appropriate cohorts.

STRATEGIES:

- Identify and develop potential domestic and foreign sites with a high seroincidence and access to populations at high risk for acquiring HIV infection, where vaccine or other prevention research activities may be feasible. This includes the following activities:
  - Track the course of the epidemic by studying HIV incidence in cohorts of individuals with high-risk behavior to identify and monitor changes in the risk profiles and infection rates (seroincidence) of various populations in the United States and worldwide; improve methods to identify and evaluate emerging risk groups and those groups most likely to be informed, willing, and capable participants in vaccine trials.
  - Develop new laboratory diagnostic tools that can be adapted for high throughput to study new HIV infections and allow distinction between vaccinees and infected individuals.
  - Analyze major histocompatibility complex (MHC) genetic differences and other relevant genetic or medical factors of populations at potential trial sites that might affect the qualitative or quantitative levels of immune responses to candidate HIV vaccines, susceptibility to infection, control of viral load, and disease progression.
  - Acquire and analyze HIV isolates from mucosal sites, as well as blood from recently infected persons representative of potential efficacy trial populations, so that genetic and antigenic information about viruses being transmitted in the population can be obtained.

- Develop and maintain the necessary immunology and virology laboratory infrastructure for conducting domestic and international vaccine efficacy trials. This includes education and training of personnel from international sites hosting vaccine trials; development of laboratory infrastructure; standardization of assays and development of panels of geographic-specific reagents composed of local, indigenous HIV+ and HIV- samples to serve as controls when validating and standardizing assays that will be used in support of clinical trials in that region; and participation of trained personnel in studies related to the trial.

- Establish, build, and nurture linkages with communities and community organizations where vaccine trials might be conducted to optimize education, recruitment, and followup activities; listen to and address community concerns and social issues, and ensure ethical conduct of AIDS vaccine efficacy trials. This includes the following:

  - For all vaccine trials, enlist participation of local representatives or community advisory boards (CABs) in the development of appropriate trial protocols as well as responsive mechanisms to inform and educate the participating individuals; establish networks within the community that will effectively, and on a continuing basis, address the social and medical concerns of the participants; establish mechanisms to provide ongoing information and open discussions concerning the scientific rationale and public health need for the study.

  - Develop mechanisms through CABs to engage collaboration and to provide education and the means to inform communities on a continuing basis so that social as well as medical concerns are addressed; work to establish trust in the community through open discussions of scientific rationale, expectations, and concerns.

  - For international trials, in addition, work closely with national (host) governmental and regulatory authorities, collaborating institutions or agencies, local community representatives, vaccine manufacturer(s), and the World Health Organization (WHO)/Joint United Nations Programme on HIV/AIDS (UNAIDS) to prepare for, plan, and conduct vaccine trials adhering to the highest ethical and scientific standards.

- In collaboration with Government agencies, institutions, NGOs, and communities being identified as potential collaborators, explore behavioral and social issues and prevention activities that might have a substantial impact on either the design or the conduct of a research trial. This includes the following research:
  - Evaluate other biomedical and behavioral interventions that could prove of benefit in decreasing the incidence of HIV infection in the populations identified for future vaccine efficacy trials; address their potential impact on the evaluation of vaccine efficacy.
  - Conduct behavioral research in populations at high risk for HIV infection to determine, for example, appropriate risk-reduction interventions and to estimate risk behavior and recruitment, adherence, unblinding, and retention strategies pertinent to the design and execution of a successful efficacy trial, especially for populations that have been historically underrepresented in clinical trials and where the epidemic is expanding disproportionately.
  - Identify and develop strategies to involve the populations with highest risk for HIV transmission in different communities; particular attention should be given to adolescents and young persons who are engaging in high-risk behaviors.
  - Collaborate with other Department of Health and Human Services (DHHS) agencies and community-based organizations to develop education programs to facilitate the conduct of Phase III HIV vaccine trials in hard-to-reach populations in domestic sites; collaborate with Walter Reed Army Institute of Research (WRAIR), the Centers for Disease Control and Prevention (CDC), the U.S. Agency for International Development (USAID), and other organizations to develop vaccine trial sites in international settings.
  - Develop appropriate communication strategies involving affected communities in the process of testing HIV vaccines and prepare for the eventual integration of preventive vaccines into comprehensive prevention and care programs in the United States and in countries where vaccine trials are conducted.
  - Determine possible adverse social, economic, behavioral, or legal consequences of participation in clinical trials; develop broadly applicable strategies for mitigating potential harm.
  - Determine optimal methods of achieving informed consent for vaccine efficacy trials.

- Explore innovative trial designs to improve efficiency of vaccine efficacy studies (e.g., determine the impact of HIV vaccines on subsequent transmission from vaccinated individuals who become infected after administration of the trial vaccine or utilizing initially concordant negative couples at high risk or discordant couples). This includes the following areas of trial design research:
  - Consider the use of secondary endpoints, particularly immune correlates of protection, surrogates of disease progression and clinical outcomes, and the benefit of long-term followup.
  - Consider the impact of early ART on HIV infections in complex trial designs.
  - Encourage linkage between vaccine preparedness studies in high-risk populations and other research activities, including research on TB and STDs; integrate research on vaccines against opportunistic infections, as appropriate.

APPENDIX A:

NIH Institutes and Centers

NIH INSTITUTES AND CENTERS

NCI	National Cancer Institute
NEI	National Eye Institute
NHLBI	National Heart, Lung, and Blood Institute
NHGRI	National Human Genome Research Institute
NIA	National Institute on Aging
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIAID	National Institute of Allergy and Infectious Diseases
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NICHD	National Institute of Child Health and Human Development
NIDCD	National Institute on Deafness and Other Communication Disorders
NIDCR	National Institute of Dental and Craniofacial Research
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NINDS	National Institute of Neurological Disorders and Stroke
NIDA	National Institute on Drug Abuse
NIEHS	National Institute of Environmental Health Sciences
NIGMS	National Institute of General Medical Sciences
NIMH	National Institute of Mental Health
NINR	National Institute of Nursing Research
NLM	National Library of Medicine
CC	Warren Grant Magnuson Clinical Center
CIT	Center for Information Technology
NCCAM	National Center for Complementary and Alternative Medicine
NCRR	National Center for Research Resources
FIC	John E. Fogarty International Center
CSR	Center for Scientific Review
NCMHD	National Center on Minority Health and Health Disparities

APPENDIX B:

FY 2005 OAR Planning Group for Vaccines

FY 2005 VACCINES PLANNING GROUP

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APPENDIX C:

List of Acronyms

LIST OF ACRONYMS

ACSR	AIDS and Cancer Specimen Resource, NCI
ACTIS	AIDS Clinical Trials Information Service
AIDS	acquired immunodeficiency syndrome
AITRP	AIDS International Training and Research Program, FIC
ART	antiretroviral therapy
ARV	antiretroviral
ATI	analytic treatment interruption
ATIS	AIDS Treatment Information Service
AVEG	AIDS Vaccine Evaluation Group
BSL	biosafety level
B/START	Behavioral Science Track Award for Rapid Transition
CAB	community advisory board
CAPS	Center for AIDS Prevention Studies (University of California, San Francisco)
CBO	community-based organization
CDC	Centers for Disease Control and Prevention
CIPRA	Comprehensive International Programs for Research on AIDS
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CTL	cytotoxic T lymphocyte
DC	dendritic cell
DHHS	Department of Health and Human Services
EBV	Epstein-Barr virus
FDA	Food and Drug Administration
GBV-C	GB virus (hepatitis G)
GCP	Good Clinical Practices
GCRC	General Clinical Research Center
GFATM	Global Fund for AIDS, Tuberculosis, and Malaria

GI	gastrointestinal
GLP/GMP	good laboratory practice/good manufacturing practice
GRIP	Global Health Research Initiative Program, FIC
HAART	highly active antiretroviral therapy
HBCU	Historically Black Colleges and Universities
HBV	hepatitis B virus
HCV	hepatitis C virus
HHV	human herpesvirus
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSV	herpes simplex virus
HVTN	HIV Vaccine Trials Network
IC	Institute and Center
ICC	invasive cervical cancer
IDU	injecting drug user
IND	investigational new drug
IRB	institutional review board
IUD	intrauterine device
JCV	JC virus
KS	Kaposi's sarcoma
KSHV	Kaposi's sarcoma herpesvirus
LRP	Loan Repayment Program, NIH
MAb	monoclonal antibody
MAC	*Mycobacterium avium* complex
MDR-TB	multidrug-resistant tuberculosis
MHC	major histocompatibility complex
MSM	men who have sex with men
MTCT	mother-to-child transmission
NAFEO	National Association for Equal Opportunity in Higher Education
NGO	nongovernment organization

NHL	non-Hodgkin's lymphoma
NHP	nonhuman primate
NIH	National Institutes of Health
NK	natural killer (cell)
NMAC	National Minority AIDS Council
NNTC	National NeuroAIDS Tissue Consortium, NIMH/NIDA/NINDS
NRTIs	nucleoside reverse transcriptase inhibitors
OAR	Office of AIDS Research, NIH
OARAC	Office of AIDS Research Advisory Council
OD	Office of the Director, NIH
OI	opportunistic infection
PACTG	Pediatric AIDS Clinical Trials Group
PCP	*Pneumocystis carinii* pneumonia
PML	progressive multifocal leukoencephalopathy
RCT	randomized clinical trial, randomized controlled trial
RNA	ribonucleic acid
RPRC	Regional Primate Research Center
SCID	severe combined immunodeficiency
SHIV	chimeric simian/human immunodeficiency virus
SIT	scheduled intermittent therapy
SIV	simian immunodeficiency virus
SPF	specific pathogen-free
STD	sexually transmitted disease
STI	structured treatment interruption; sexually transmitted infection
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	U.S. Agency for International Development
VRC	Vaccine Research Center
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WRAIR	Walter Reed Army Institute of Research

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